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PATENT
Docket No.: **19603/1453 (CRF D-2008B)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Xin-Yun Huang	Examiner: N.S. Basi
Serial No.	:	09/273,217	
Cnfrm. No.	:	6809	Art Unit: 1646
Filed	:	March 19, 1999	
For	:	METHODS FOR IDENTIFYING SPECIFIC ION CHANNEL BLOCKERS	

DECLARATION OF XIN-YUN HUANG UNDER 37 C.F.R. § 1.132

U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202
Box:

Dear Sir:

I, XIN-YUN HUANG, pursuant of 37 C.F.R. § 1.132, declare:

1. I received a B.S. degree in Biology from Wuhan University, Wuhan, Hubei, P.R. China in 1983 and a Ph.D. degree in Biochemistry from the University of Houston, Houston, Texas in 1988.

2. I am currently employed as Professor of Physiology and Biophysics at Cornell University, Weill Medical College, New York, New York.

3. I am the inventor of the above-identified application.

4. I am presenting this declaration to show (1) that it is well recognized in the art that external vestibules of all potassium, calcium, and sodium channels have similar structures, and (2) that it has been demonstrated that inhibition of ion channel activity is due to binding of a blocking agent (e.g., an antibody) to a particular peptide sequence located in the external vestibule of an ion channel.

5. As evidenced by various publications involving ion channel investigations, it is accepted in the field of expertise that external vestibules of all potassium, calcium, and sodium channels have similar structures. See Doyle et al., "The Structure of the Potassium Channel: Molecular Basis of K^+ Conduction and Selectivity," Science 280:69-77 (1998) ("Doyle") (attached hereto as **Exhibit 1**); MacKinnon et al., "Structural Conservation in Prokaryotic and Eukaryotic Potassium Channels," Science 280:106-109 (1998) ("MacKinnon") (attached hereto as **Exhibit 2**); and Lu et al., "Ion Conduction Pore Is Conserved Among Potassium Channels," Nature 413:809-813 (2001) ("Lu") (attached hereto as **Exhibit 3**). Because of the structural similarity of the external vestibules of ion channels, it is not necessary to know which part of the ion channel constitutes the external vestibule in order to practice the methods of the present invention. This is evidenced by the use of the claimed technology to inhibit a store-operated Ca^{2+} channel, as reported in Xu et al., "TrpC1 Is a Membrane-Spanning Subunit of Store-Operated Ca^{2+} Channels In Native Vascular Smooth Muscle Cells," Circulation Research 88:84-87 (2001) ("Xu") (attached hereto as **Exhibit 4**).

6. Although most potassium channels do, indeed, have six transmembrane regions, even ion channels (including potassium channels) with less than six transmembrane regions have regions equivalent to the S5 and S6 regions (also referred to as M1 and M2 regions) as described in the present application. See Jan et al., "Cloned Potassium Channels From Eukaryotes and Prokaryotes," Ann. Rev. Neurosci. 20:91-123 (1997) ("Jan") (attached hereto as **Exhibit 5**). Thus, with regard to targeting of the external vestibule of an ion channel to inhibit the activity of the ion channel, it is of no consequence that all ion channels do not have six transmembrane regions

7. Experimental data has shown that the binding of a blocking agent (e.g., an antibody) to the external vestibule portion of the ion channel results in the inactivation of the ion channel. For example, as reported by my laboratory, experimental tests have shown that the antibody blocking effect of an ion channel's functionality could be attenuated by preincubating the antibody with an immunogenic peptide, but not with a control peptide (Zhou et al., "Specific Antibodies to the External Vestibule of Voltage-Gated Potassium Channels Block Current," J. Gen. Physiol. 111:555-563 (1998) ("Zhou") (attached hereto as **Exhibit 6**)). The data presented in Zhou demonstrated that the inhibition of the ion channel's activity is due to specific binding of an antibody to a particular peptide sequence located in the external vestibule.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2/26/03

Xin-Yun Huang